Cycloadditions of Cyanoketenes to Cinnamylideneamines and Benzylideneamines. Synthetic Scope, Stereochemistry, and Mechanism

Harold W. Moore,* Gregory Hughes, Kasturi Srinivasachar, Mario Fernandez, Nghi V. Nguyen, Doug Schoon, and Anne Tranne

Department of Chemistry, University of California, Irvine, California 92717

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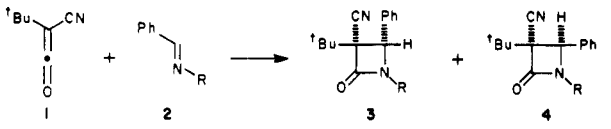
A study of the cycloadditions of cyanoketenes [*tert*-butylcyanoketene (TBCK), chlorocyanoketene (CCK), and hexynylcyanoketene (HCK)] to cinnamylideneamines and benzylideneamines is presented. The size and degree of unsaturation of the imine substitutents were varied in order to probe those factors that influence both stereo- and periselectivity of the cycloadditions. In the cinnamylidene series, it was generally found that 2-azetidinone formation is enhanced when the N-substituent of the imine is small. In general, the stereochemistry of the 2-azetidinone can be controlled by the bulk of this substituent as well as the substitution pattern of the imine. Within the benzylidene series, the cycloadditions are stereospecific when the N-substituent is an aryl group; only 3-cyano-2-azetidinones having a trans relationship between the 3-cyano group and the proton at position 4 are observed. However, as the steric bulk of this substituent is increased, the yield of the corresponding cis diastereomer progressively increases. These results are discussed in terms of a two-step zwitterionic mechanism.

In this paper we describe an investigation of the cycladditions of cyanoketenes to cinnamylideneamines and benzylideneamines. The prime objective in initiating this work was to provide a systematic study of the cycloadditions of bona fide ketenes to imines. Surprisingly, such an investigation has not previously appeared even though ketene/imine cycloadditions are the most widely employed synthetic route to 2-azetidinones and have been under study for more than 75 years.[1] Cyanoketenes are obvious candidates for such a study since they are unsymmetrical, highly reactive, and readily available and can be generated under neutral conditions.[2] This last point is of particular note since many prior studies have concerned the reactions of imines with acid halides in the presence of tertiary amines, and the results are confusing with respect to mechanism and stereochemical outcome.[3] Some of the trends of these previously reported studies are outlined below.

Acid halide/imine reactions are of general synthetic importance as a route to 2-azetidinones when the α-position of the acid halides bears an anion-stabilizing substituent, i.e., halo,[4-7] azido,[8] alkoxy,[4,9-11] and carbonyl halide.[9,12] However, it is often difficult to confidently predict the stereochemistry of the product. For example, some reports describe the cycloadditions to be stereospecific[7,9,10] while others observe mixtures of *cis*- and *trans*-2-azetidinones.[5] In addition, the degree of stereospecificity genrally depends upon the experimental condition employed.[8] For example, products having trans stereochemistry appear to be preferred when the amine is added to a solution of the acid halide and imine, while cis products often predominate when the acid halide is added to a solution of the amine and imine. It is not completely clear whether either of these methods involve a bona fide ketene intermediate or even if the tertiary amine or its conjugate acid have an influence on product stereochemistry. However, it is generally assumed that the latter method involves a ketene intermediate and the former an acyliminium ion.[13]

Scheme I



1 2 3 4

	R	% 3 (mp)	% 4 (mp)	% Total
a	C_6H_5	* 86 (204-205)	—	86
b	C_6H_4-p-Cl	* 89 (193-194)	—	89
c	C_6H_4-p-OCH_3	* 93 (182-183)	—	93
d	n-C_4H_9	* 82 (119-120)	—	82
e	c-C_6H_{11}	* 94 (154-155)	—	94
f	t-C_4H_9	* 19 (165-166)	*72 (175-176)	91

* Satisfactory Elemental Analysis

Most of the reported ketene/imine cycloadditions involving a true ketene are for diphenylketene[14-16] and dimethylketene.[17,18] However these cycloadditions lack an important stereochemical probe since the ketenes are symmetrical. Therefore, the study described here was initiated by employing unsymmetrical cyanoketenes, a class of cumulenes which are easily generated under neutral conditions upon thermolysis of 2,5-diazido-1,4-benzoquinones or 4-azido-2-furanones. The specific ketenes employed were *tert*-butylcyanoketene (TBCK),[19] chlorocyanoketene (CCK),[20] and hexynylcyanoketene (HCK),[21] thus providing a series that differs in both steric bulk and electrophilicity. The imines employed were cinnamylideneamines and benzylideneamines, and the

(1) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51.
(2) Moore, H. W.; Gheorghiu, M. D. *Chem. Soc. Rev.* **1981**, *10*, 289.
(3) See, for example: Isaacs, N. S. *Chem. Soc. Rev.* **1976**, *4*, 181.
(4) Lattrell, R.; Lohaus, G. *Chem. Abstr.* **1972**, *77*, 48, 159.
(5) Nelson, D. A. *J. Org. Chem.* **1972**, *37*, 1447.
(6) Muderdzhi, A. K.; Savarov, N. N. *Khim. Geterotsilkl. Soedin.* **1970**, 1626.
(7) Bose, A. K.; Dayal, B.; Chawla, H. P. S.; Manhas, M. S. *Tetrahedron Lett.* **1972**, 2823.
(8) Bose, A. K.; Anjaneyulu, C.; Shattacharya, S. K.; Manhas, M. S. *Tetrahedron* **1967**, *23*, 4769.
(9) Bose, A. K.; Spiegelman, G.; Manhas, M. S. *Tetrahedron Lett.* **1971**, 3167.
(10) Bose, A. K.; Lai. B.; Dayal, B. *Tetrahedron Lett.* **1974**, 2633.
(11) Lattrill, R.; Lohaus, G. *Justus Liebigs Ann. Chem.* **1974**, 87.
(12) Bose, A. K.; Kapur, J. C.; Dayal, B.; Manhas, M. S. *J. Org. Chem.* *39*, 312.
(13) Duran, F.; Ghosez, L. *Tetrahedron Lett.* **1970**, 245.
(14) Decazes, J. M.; Juche, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1970**, 3661, 3665.
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(19) Weyler, W.; Duncan, W. G.; Moore, H. W. *J. Am. Chem. Soc.* **1975**, *97*, 6187.
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(21) Nguyen, N.; Moore, H. W. *J. Chem. Soc., Chem. Commun.* **1984**, 1066.

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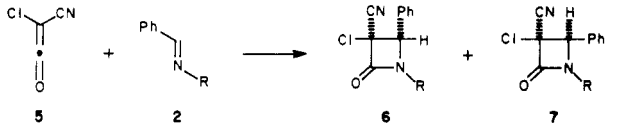
Scheme II

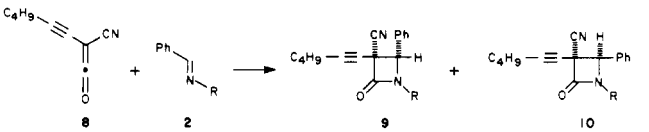


5 2 6 7

	R	% 6 (mp)	% 7 (mp)	% Total
a	C_6H_5	* 88 (146-147)	—	88
b	C_6H_4pCl	* 95 (oil)	—	95
c	C_6H_4-p-OCH_3	* 93 (98-99)	—	93
d	n-C_4H_9	* 92 (83-84)	—	92
e	c-C_6H_{11}	* 81 (116-117)	19	97
f	t-C_4H_9	—	*88 (87-88)	88

* Satisfactory Elemental Analysis
* Satisfactory High Resolution MS

Scheme III



8 2 9 10

	R	% 9 (mp)	% 10 (mp)	% Total
a	C_6H_5	* 81 (119-120)	—	81
b	C_6H_4-p-Cl	* 80 (128-130)	trace	80
c	C_6H_4-p-OCH_3	* 75 (119-120)	trace	72
d	n-C_4H_9	* 65 (oil)	trace	62
e	c-C_6H_{11}	* 69 (oil)	21 (oil)	89
f	t-C_4H_9	14 (oil)	*51 (82-83)	65

* Satisfactory Elemental Analysis
* Satisfactory High Resolution MS

specific substitution pattern of these were varied to introduce a controlled range of steric bulk. The cinnamylidene series presented an additional variable of interest, i.e., the degree of unsaturation. In this regard, it was of interest to determine those factors that control not only the stereoselectivity but also the periselectivity of the cycloadditions, particularly those factors that would enhance 2 + 2 cycloadditions to give β-lactams vs. 2 + 4 cycloadditions to give δ-lactams.[22]

The results obtained and presented here are of interest with respect to the synthetic design of 3-cyano-2-azetidinones as well as of mechanistic importance regarding the dipolar cycloadditions of electron-deficient ketenes to imines. Most importantly, a mechanistic paradigm is presented which allows predictions of stereo-, regio-, and periselectivity of these dipolar cycloadditions and, by implication, others which have previously appeared in the literature.

Results

The cycloadditions represented in Schemes I–VI were accomplished by generating 1.0 equiv of the respective ketene in refluxing benzene in the presence of 1.0 equiv of the imine. The precursors for the ketenes TBCK (1), CCK (5), and HCK (8) were respectively 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone, 4-azido-3-chloro-5-methoxy-2-furanone, and 2,5-diazido-3,6-dihexynyl-1,4-benzoquinone. These have previously been shown to provide the corresponding ketenes upon thermolysis in refluxing benzene.[19-21] The imines were prepared by treating a CH_2Cl_2 solution of the respective aldehyde with the amine in the presence of anhydrous magnesium sulfate.[23]

The data provided in Schemes I–VI show the following significant trends: (1) High yields of 2-azetidinones are reported for all of the cycloadditions. (2) When the cycloadditions were nonstereospecific, the major diastereomer was generally that in which the 3-cyano group and the proton at position 4 are in a trans relationship. (3) The stereoselectivity of all of the cycloadditions resulting in 2-azetidinones is directly related to the steric bulk of the N-substituent of the imine. Generally, as this substituent increases in size, the yield of the resulting 2-azetidinone having a cis relationship between the 3-cyano and 4-protio groups increases. (4) Periselectivity in the ketene/cinnamylideneamine series is dependent upon the steric bulk of both the ketene and imine. For example, TBCK generally results in 2 + 2 cycloadducts (β-lactams) as the major or exclusive products, while the less bulky CCK and HCK give primarily 2 + 4 cycloadducts (δ-lactams). However, all of the ketenes cycloadd to the β-phenylcinnamylideneamines to give β-lactams as the exclusive or major products.

The structures and stereochemistry of the products were established on the basis of spectral, chemical, and X-ray data. The stereostructure of the 3-chloro-3-cyano-2-azetidinones **15a–d,i–k** and **18k,l**, were assigned as follows (Scheme VII). The β-lactams **15c,d,i** were dechlorinated (Zn/CH_3CO_2H), and the resulting β-lactams were converted to their enolates (NaH, THF). These were then treatd with *N*-chlorosuccinimide, which results in a mixture of the starting 3-chloro-3-cyano-2-azetidinones, **15c,d,i**, and their respective diastereomers, **21c,d,i** and in all cases the major isomer was identical with the initial starting β-lactam.[24] Thus, if one assumes that the chlorination takes place from the less hindered side of the enolate anions, the assigned stereochemistry of **15c,d,i** are firmly established. This assignment was further confirmed from the ^1H NMR spectra of **15c,d,i** and their corresponding diastereomers. That is, it has previously been shown that the methine proton at position 4 in 3-cyano-2-azetidinones is deshielded when disposed cis relative to trans to the 3-cyano substituent.[25] The chemical shifts of this proton in **15c,d,i** appear at δ 4.88, 4.37, and 4.73, while those of their respective diastereomers **21c,d,i** appear at δ 5.13, 4.68, and 5.00. This deshielding effect was also employed to assign the stereochemistry of **15k** and **18k**; the former shows its methine proton at δ 4.30 and the latter at δ 4.57. The β-lactam **18l** was also subjected to a dechlorination–rechlorination sequence (Scheme VIII). However, as expected from the assigned stereochemistry of **18l** the major product was the diastereomer **23**; the chemical shift of the methine proton in **18l** appears at δ 4.57 and that for **23** at δ 4.26. The ratio of products **23** and **18l** was 2:1, and this same ratio was also obtained when **23** was subjected to the

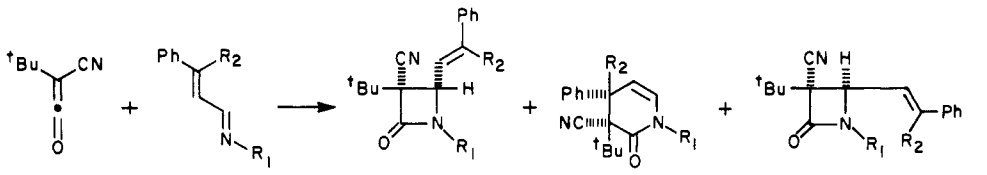
(22) For other reports of the reactions of acyl halides with cinnamylideneamines, see: (a) Just, G.; Ugolini, A.; Zamboni, R. *Synth. Commun.* **1979**, *9*, 117. (b) Duran, F.; Ghosez, L. *Tetrahedron Lett.* **1970**, 245. (c) Kametani, T.; Yokohama, S.; Shiratori, Y.; Satoh, F.; Ihara, M.; Fukumoto, K. *Heterocycles* **1979**, *12*, 669. (d) Doyle, T. W.; Balleau, B.; Luh, B. Y.; Ferrari, C. F.; Cunningham, M. P. *Can J. Chem.* **1977**, *55*, 468. (e) Doyle, T. W.; Belleau, B.; Luh, B. Y.; Conway, T. T.; Menard, M.; Douglas, J. L.; Chu, D. T. W.; Lin, G.; Morris, L. R.; Revest, P.; Casey, M. *Ibid.* **1977**, *55*, 468. (f) Doyle, T. W. *Ibid.* **1977**, *55*, 2714. (g) Brady, W. T.; Shieh, C. H. *J. Org. Chem.* **1983**, *48*, 2499.

(23) Daegusa, T.; Kobayashi, S.; Hirota, K.; Okumusa, Y.; Ito, Y. *Bull. Soc. Chem. Jpn.* **1968**, *41*, 1638.

(24) This procedure has been previously employed to establish the stereochemistry of selected β-lactams in the cinnamylidene series. See: Moore, H. W.; Hughes, G. *Tetrahedron Lett.* **1982**, 4003.

(25) See, for example: (a) Reference 20. (b) Chambers, R.; Kunert, D. M.; Hernandez, L.; Mercer, F.; Moore, H. W. *Tetrahedron Lett.* **1978**, 933. (c) Weyler, W.; Byrd, L. R.; Caserio, M. C.; Moore, H. W. *J. Am. Chem. Soc.* **1972**, *94*, 1027.

Scheme IV



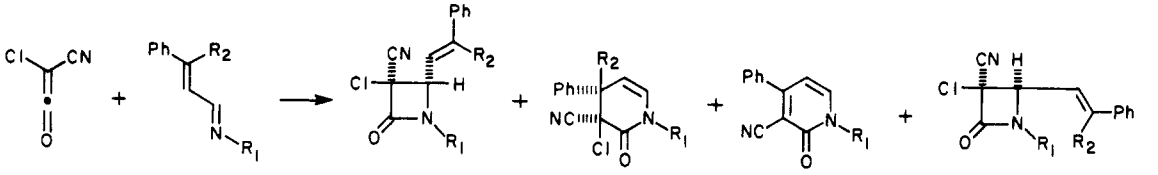
1 11 12 13 14

	R_1	R_2	% 12 (mp)	% 13	% 14	% Total
a	C_6H_5	H	*82 (199-201)	—	—	82
b	C_6H_4-p-Cl	H	*76 (157-158)	*12 (163-164)	—	88
c	C_6H_4-p-OCH_3	H	*95 (201-202)	—	—	95
d	n-C_4H_9	H	*62 (99-100)	—	—	62
e	c-C_6H_{11}	H	*63 (190-191)	*23 (161-162)	* 5 (123-125)	91
f	t-C_4H_9	H	*16 (206-207)	*47 (oil)	*20 (148-149)	83
g	C_6H_5	C_6H_5	*77 (168-169)	—	—	77
h	C_6H_4-p-Cl	C_6H_5	*74 (oil)	—	—	74
i	C_6H_4-p-OCH_3	C_6H_5	*92 (oil)	—	—	92
j	n-C_4H_9	C_6H_5	*97 (oil)	—	—	97
k	c-C_6H_{11}	C_6H_5	*83 (114-116)	—	—	83
l	t-C_4H_9	C_6H_5	*58	—	*32	90**

* Satisfactory Elemental Analysis

** Mixture of Diasteriomers

Scheme V



5 11 15 16 17 18

	R_1	R_2	% 15	% 16	% 17	% 18	% Total
a	C_6H_5	H	* 9 (166-167)	*26 (163-164)	36 (190-191)	—	71
b	C_6H_4-p-Cl	H	*22 (137-138)	*37 (170-171)	*24 (249-250)	—	83
c	C_6H_4-p-OCH_3	H	*17 (127-126)	*42 (142-143)	*22 (193-194)	—	81
d	n-C_4H_9	H	7 (oil)	54 (oil)	*14 (133-134)	—	75
e	c-C_6H_{11}	H	—	*70 (168-169)	*20 (210-211)	—	90
f	t-C_4H_9	H	—	*56 (104-106)	*19 (181-182)	—	75
g	C_6H_5	C_6H_5	*82 (oil)	—	—	—	82
h	C_6H_4-p-Cl	C_6H_5	88 (oil)	—	—	—	88
i	C_6H_4-p-OCH_3	C_6H_5	*91 (133-135)	—	—	—	91
j	n-C_4H_9	C_6H_5	68 (oil)	—	—	—	68
k	c-C_6H_{11}	C_6H_5	*20	*36 (134-135)	—	*38	94**
l	t-C_4H_9	C_6H_5	—	—	—	*86 (140-141)	86

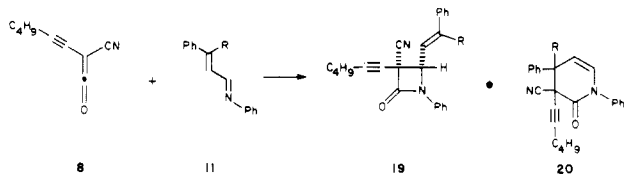
* Satisfactory Elemental Analysis

** Mixture of Diasteriomers

dechlorination–rechlorination sequence. On the basis of these data, the remaining 3-chloro-3-cyano-4-(2-phenylethenyl)- and -(2,2-diphenylethenyl)-2-azetidinones have been assigned the *E* stereochemistry as generally represented by structure **15**.

The stereochemical assigments of the 3-cyano-2-azetidinones **3**, **4**, **6**, **7**, **9**, **10**, and **19** were all made on the basis of the chemical shift of the methine proton at position 4. In each case where a comparison was possible, the chemical shift of this proton appeared at a more deshielded position

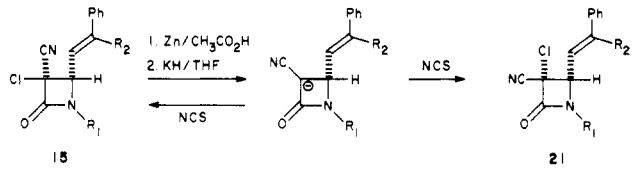
Scheme VI



R	%19 (mp)	%20 (mp)	% TOTAL
H	* 9 (oil)	* 62 (oil)	71
C_6H_5	* 52 (oil)	* 19 (oil)	71

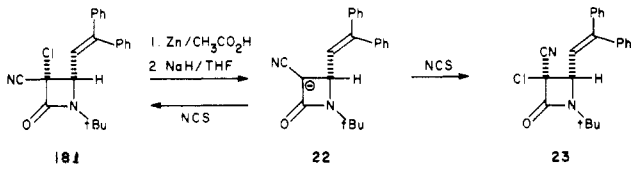
* Satisfactory High Resolution MS

Scheme VII



R_1	R_2	RATIO 15:21
C_6H_4-p-OCH_3	H	7:4
nC_4H_9	H	9:5
C_6H_4-OCH_3	C_6H_5	8:5

Scheme VIII



RATIO 23:18*l* = 2:1

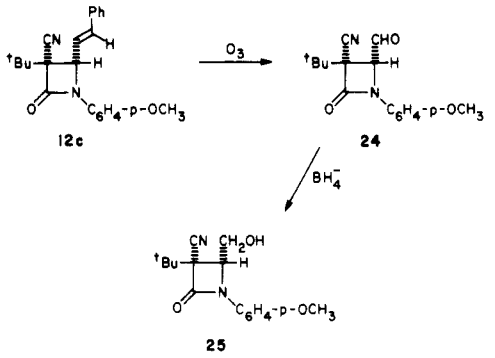
in the diastereomer having the proton and cyano group cis disposed.

The same ^1H NMR argument was employed to assign the stereostructure of the diastereomeric pairs of the 3-*tert*-butyl-3-cyano-2-azetidinones, **12e** and **14e**, **12f** and **14f**, and **12l** and **14l**. However, in this series it was also deemed necessary to establish the stereochemistry of at least one example by a single-crystal X-ray analysis since a chemical interconversion study as utilized in the 3-chloro series was not possible. To this end, the β-lactam **12c** was chosen. However, since crystals of **12c** that were satisfactory for X-ray studies could not be obtained, it was converted to a derivative that was amenable to such a study (Scheme IX). Ozonolysis of **12c** gave the aldehyde **24**, which was not isolated but immediately subjected to reduction with sodium borohydride to give 3-*tert*-butyl-3-cyano4-(hydroxymethyl)-1-(4-methoxyphenyl)-2-azetidinone **25** as a white crystalline solid. The complete X-ray structure was determined, which revealed the *Z* configuration as illustrated by structure **25**.[26] Thus the assigned stereochemistry of the β-lactam **12c** appears to be on firm ground.

The above data were used as the foundation for the general assumption that the alkylcyanoketene (TBCK) cycloadds to cinnamylideneamines to give the stereoisomer represented by the general structure **12** as the major β-

(26) We wish to thank Professor Robert Doedens, Department of Chemistry, University of California, Irvine, CA, for the X-ray structural determination.

Scheme IX

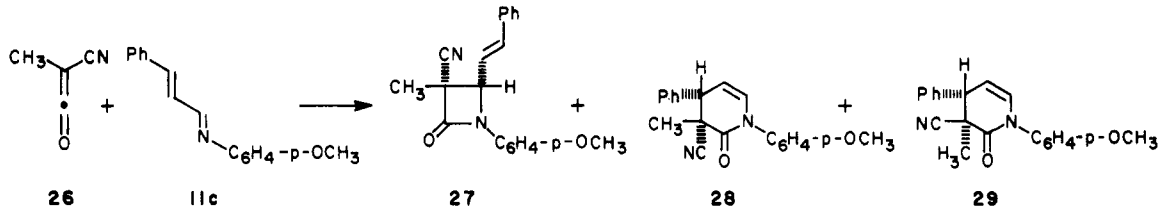


lactam products. This was further probed by investigating the cycloaddition of the less bulkyl homologue, methylcyanoketene (**26**) to **11c** (Scheme X). In this case, the observed products were the β-lactam **27** and the two δ-lactams **28** and **29**. The stereochemistry of **27** was readily assigned by the declorination/methylation sequence outlined in Scheme XI. That is, methylation of the enolate **30** from the least hindered face gave only the β-lactam **27**. Analogously, methylation of the enolate **31** gave only the δ-lactam **28**, and thus the stereochemistry of both **28** and its diastereomer **29** were obtained (Scheme XII).

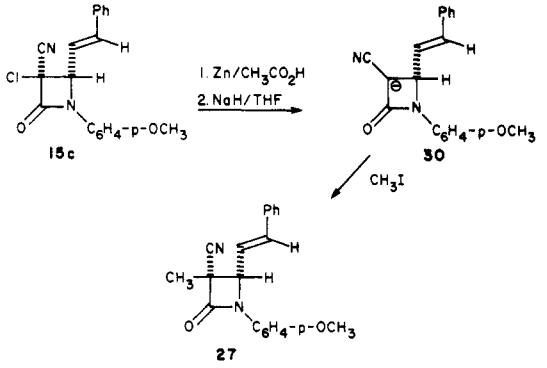
The assigned *E* stereochemistry of the δ-lactams **16a–f** is based upon arguments analogous to those used above; e.g., treatment of the enolate **31** with NCS regenerated **16c** in >90% yield (Scheme XII). In addition, the *E* stereochemistry of **16c** prevents it from undergoing facile dehydrochlorination upon treatment with triethylamine. The δ-lactam **16e** behaved analogously when treated with the amine. Thus, the δ-lactams obtained in the CCK cycloaddition are all assumed to have the stereochemistry represented by the general structure **16**. It is also reasonable to assume that the diastereomers of **16a–f** are also formed under the reaction conditions. However, such compounds would now have the *Z* stereochemistry and undergo facile dehydrochlorination under the reaction conditions to give the respective pyridones **17a–f**. This assumption is supported by the results of the cycloaddition of methylcyanoketene to **11c** (Scheme X). That is, both diastereomers **28** and **29** are formed, but obviously neither of these can undergo an elimination reaction. Furthermore, the major isomer is **28**, which is stereochemically analogous to **16c**, the major product from the related cycloaddition of CCK to **11c**.

The assigned stereochemistry of the δ-lactams **13d–f** is more difficult to establish since they are not directly amenable to a simple chemical or spectral probe. However, the indicated *Z* configuration seems reasonable on the basis of indirect arguments. For example, since the major δ-lactam formed in the CCK and methylcyanoketene cycloadditions can be assigned as **16** and **28**, respectively, it is expected that the TBCK cycloadditions would give analogous products but perhaps more selectively due to steric considerations either at the product or transition-state level. Indeed, only one β-lactam isomer, i.e., **13**, is formed in the TBCK cycloaddition, while both diastereomers result from the CCK and methylcyanoketene reactions. In addition, supporting evidence is obtained by comparing the ^1H NMR data obtained for **13d–f** with those for the β-lactams **28** and **29**. For example, the methine proton of **29** (δ 3.94) is deshielded compared with that of **28** (δ 3.70). Thus, as in the β-lactam series, the methine proton of **29** experiences a deshielding caused by the anisotropy effect of the cis cyano group. The chemical shifts of the corresponding proton in **13d–f** appear at respectively

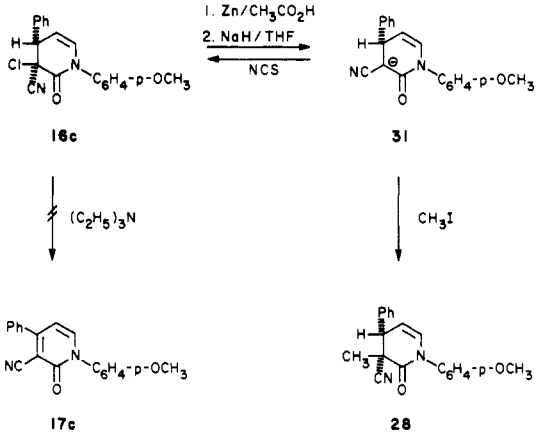
Scheme X



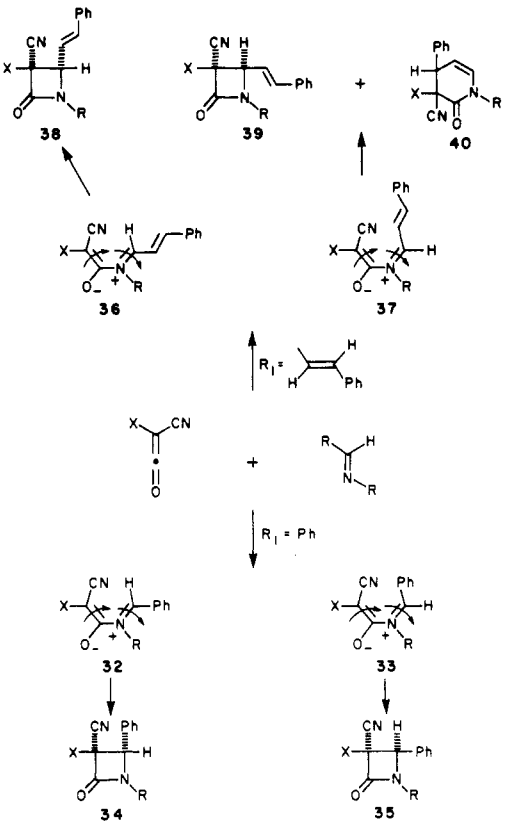
Scheme XI



Scheme XII



Scheme XIII



δ 3.75, 3.76, and 3.68. These shifts are internally consistent for these compounds to be of the same configuration and also compare favorably with that observed for **28**, a compound of known configuration. Thus, their stereostructures are assigned as indicated.

Mechanism

The results thus far presented allow the formulation of a mechanistic model. First of all, a two-step zwitterionic mechanism rather than a concerted cycloaddition is clearly in operation. This conclusion is based upon the observation of both 2 + 2 and 2 + 4 products in the ketene/cinnamylideneamine cycloadditions as well as upon analogies established in work previously presented from this laboratory on cyanoketene/formimidate cycloadditions.[27-30] Furthermore, it is noted that an intense purple color is observed when a toluene solution of **11f** is treated with TBCK at −78 °C; this color, which is assumed to be due to the zwitterionic intermediate, gradually fades as the reaction solution is allowed to warm to ambient temperature, and the cycloadducts **12f**, **13f**, and **14f** are the observed products.

A stepwise pathway that accounts for the observed stereo-, regio-, and periselectivity of the cycloadditions is outlined in Scheme XIII. Specifically, for the cyanoketene/benzylideneamine cycloadditions the zwitterions **32** and **33** lead to the respective 2-azetidinones **34** and **35** and are proposed to do so upon conrotatory ring closure. The zwitterions **32** and **33** are those in which steric interactions have been minimized. That is, the smaller substituent of the ketene (CN) is endo oriented and the larger group (Cl) is exo. However, the relative proportions of the zwitterions and thus also the 2-azetidinone products are significantly influenced by the bulk of the N-substituent. That is, when R is small, zwitterion **32** is greatly favored since the phenyl/cyano interaction is relieved, and thus 2-azetidinone **34** results as the major or exclusive product. However, as R becomes larger its steric interaction with the adjacent phenyl group in **32** increases, and thus the concentration of **33** also increases. Ultimately, as in the case of the CCK/**2f** cycloaddition, the abovementioned steric interaction in **32** becomes much greater than that of the phenyl/cyano interaction in **33**, and thus

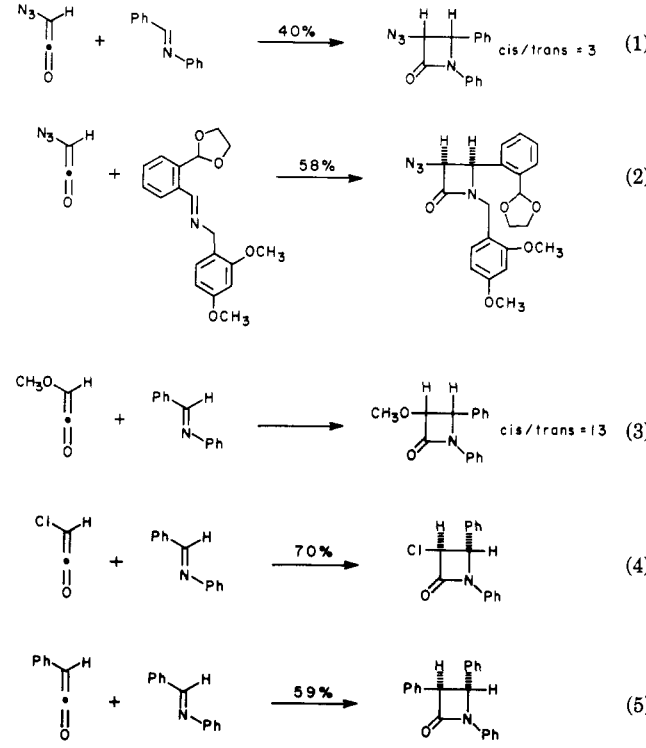
(27) Kunert, D. M.; Chambers, R.; Mercer, F.; Hernandez, L.; Moore, H. W. *Tetrahedron Lett.* **1978**, 929.
(28) Moore, H. W.; Hernandez, L.; Chambers, R. *J. Am. Chem. Soc.* **1978**, *100*, 2245.
(29) Moore, H. W. *Acc. Chem. Res.* **1979**, *12*, 125.
(30) It is further noted that a zwitterionic intermediate in a diphenylketene/imine cycloaddition has recently been detected by matrix isolation. See: Pacansky, J.; Chang, J. S.; Brown, D. W.; Schwarz, W. *J. Org. Chem.* **1982**, *47*, 2233.

2-azetidinones of stereostructure **35** become the favored product. With the more bulky TBCK, the zwitterion analogous to **32** is generally more favored than in the CCK or HCK cycloadditions. This is reasonable since the configuration of such a zwitterion would maintain the greatest distance between the *tert*-butyl group of the ketene and the phenyl group of the imine. In the most extreme case, TBCK/**2f** cycloaddition, the intermediate analogous to **33** is favored but not exclusively since some of the 2-azetidinone corresponding to **34**, i.e., **3f**, is still formed as a minor product.

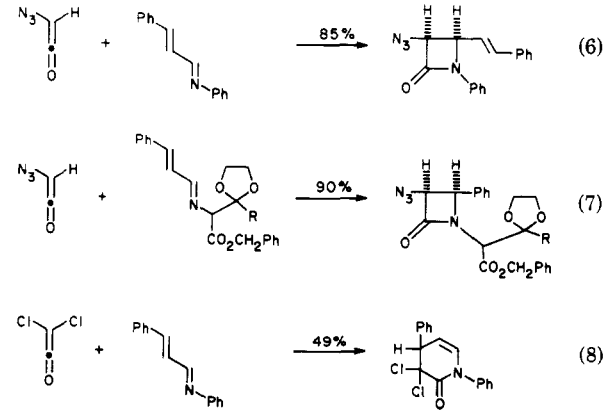
The results obtained with the cyanoketene/cinnamylideneamines are also in agreement with the mechanism presented in Scheme XIII. For example, the 2-phenylethenyl group provides an alternate reaction pathway from zwitterion **37**, i.e., ring closure to form a six-membered ring rather than a four-membered ring analogue. This reaction pathway is apparently favored over other possible routes for the small ketenes CCK and HCK since these ketenes cycloadd to the cinnamylideneamines to give the 2 + 4 cycloadducts (40) as the major products. In this regard, it is also noteworthy that **37** ring closes to give only the six-membered lactam since no β-lactam corresponding to **39** was observed in these cycloadditions. The analogous cycloadditions involving the bulky TBCK proceed predominately via zwitterion **36** rather than **37** to give β-lactams of the general stereostructure **38**. Again, this is reasonable since steric repulsions between the bulky *ter*-butyl group and the 2-phenylethenyl group would be minimized in zwitterion **36**. However, as was the case for the TBCK/benzylideneamine cycloadditions, the concentrations of zwitterion **37** and its corrresponding products **39** and **40** are enhanced as the steric bulk of the N-substituent (R) increases.

Finally, it is noted that the periselectivity of the cyanoketene/cinnamylideneamine cycloadditions is dramatically affected by the substitution pattern at the β-position of the imine. Specifically, the cinnamylideneamines **11g–l** cycloadd to TBCK, CCK, and HCK to give β-lactams corresponding to stereostructure **36** as the major or exclusive product, a result analogous to that observed for the benzylideneamine series. The additional phenyl substituent at the β-position of these imines apparently retards the ring closure of the zwitterion corresponding to **37** and thus enhances the analogous **36** → **38** pathway. However, as with the previously discussed examples, increasing the bulk of the N-substituent of the imine can ultimately favor the **37** → **39** and **40** pathway. The most impressive comparison in this regard are the cycloadditions of CCK to respectively **11c**, **11i**, and **11l**; the first two give the corresponding 2-azetidinones **15c** and **15i** in respective yields of 17% and 91%, while the bulky **11l** gives exclusively the 2-azetidinone **18l** (86%), a 2-azetidinone having opposite stereochemistry.

In conclusion, the above mechanistic paradigm involves arguments in which steric interactions within the zwitterions **32**, **33**, **36**, and **37** are minimized and that these intermediates proceed to 2-azetidinones via a conrotatory ring closure. It is noteworthy that such simple arguments can also be employed to explain a number of other ketene/imine cycloadditions that have previously been reported. In this regard, some specific observations and predictions are listed in the following: (1) *cis*-2-Azetidinones, arising from zwitterions analogous to **33** (CN=H), would be favored from the cycladditions of small monosubstitued ketenes (e.g., azido- and methoxyketene) to benzylideneamines. This cis selectivity may dominate regardless of the steric bulk of the N-substituent of the imine, but it should increase as the bulk of this substituent increases (eq 1–3). (2) Apparently, monosubstituted



ketenes bearing a substituent larger than a methoxy group give primarily *trans*-2-azetidinones, products arising from zwitterions analogous to **32** (CN=H) (eq 4–5). (3) For disubstituted ketenes (e.g., CCK), 2-azetidinones arising from zwitterions analogous to **32** would be favored when the imine substituents are small. However, a reversal of stereochemistry can conceivably be induced by increasing the bulk of N-substituent and thus favoring zwitterion **33** (Schemes I and II). Such a reversal would, of course, also depend upon the relative size of the ketene substituents, i.e., the larger the less likely. (4) *cis*-2-Azetidinones are favored from the cycloadditions of the small azidoketene with cinnamylideneamines (eq 6–7). Apparently, with this



ketenes, a completely planar zwitterion analogous to **33** can result and conrotatory ring closure to β-lactams is favored over ring closure to a δ-lactam. For the disubstituted ketenes such as CCK, HCK, and dichloroketene a completely planar zwitterion is not possible, and thus ring closure to a six-membered ring is favored (eq 8, Schemes V and VI). (5) When the β-position of the cinnamylideneamine is disubstituted, ring closure to a δ-lactam is inhibited. In such cases, the results are analogous to those observed for ketene/benzylideneamine cyclo-

additions, i.e., conrotatory ring closure of **36** (Schemes V and VI).

Experimental Section

Cycloadditions of *tert*-Butylcyanoketene to Benzylideneamines. General Procedure. A solution of 160 mg (0.5 mmol) of 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone and 1.0 mmol of the imine in 30 mL of anhydrous benzene was refluxed for 2 h. The solvent was then removed in vacuo, and the residue was triturated with ether–hexane to yield the crystalline 2-azetidinones. The mother liquor was then subjected to preparative TLC to yield additional product. The resulting β-lactams all showed spectral properties (IR, NMR, and MS) that are characteristic with their assigned structures. See paragraph at end of text about supplementary material.

Cycloadditions of Chlorocyanoketene to Benzylideneamines. General Procedure. These cycloadditions were accomplished in analogy to those using TBCK. However, the ketene precursor was 4-azido-3-chloro-5-methoxy-2-furanone, and the reaction time was approximately 6 h. The solvent was removed in vacuo and the residue purified by preparative TLC (silica gel, 1:9 ethyl acetate–hexane). Spectral and physical properties for the products of these reactions are in agreement with their assigned structures. See paragraph at end of text about supplementary material.

Cycloadditions of Hexynylcyanoketene to Benzylideneamines. General Procedure. A solution of 200 mg of 2,5-diazido-3,6-dihexynyl-1,4-benzoquinone[21] (0.57 mmol) in 50 mL of dry benzene was added dropwise to a refluxing solution of 1.0 mmol of the imine in 150 mL of benzene under nitrogen. After approximately 3 h, the solvent was removed in vacuo, and the residue was purified by silica gel chromatography (hexane–ethyl acetate). Spectral and analytical properties of the resulting 3-cyano-3-(1-hexynyl)-2-azetidinones are in agreement with their assigned structures. See paragraph at end of text about supplementary material.

Cycloadditions of *tert*-Butylcyanoketene to Cinnamylideneamines 11a–l. General Method. A solution of 333 mg (1.1 mmol) of 2,5-diazido-3,6-di-*tert*-butyl-1,4-benzoquinone and 2.0 mmol of the imine in 25 mL of anhydrous benzene was refluxed for 4 h. The solvent was removed in vacuo, and the residue was purified by preparative chromatography (silica gel, 1.5:8.5 ethyl acetate–hexane). Spectral and physical properties of the products of these reactions are in agreement with their assigned structures. See paragraph at end of text for supplementary material.

Cycloadditions of Chlorocyanoketene to Cinnamylideneamines 11a–l. General Procedure. These cycloadditions were accomplished in analogy to those using TBCK. However, the ketene precursor was 4-azido-3-chaloro-6-methoxy-2-furanone, and the reaction time was approximately 12 h. At the end of this time most of the reaction solutions became dark in color. However, this is due to minor impurities, and the color can be removed by rapid filtration through silica gel. Spectral properties for the cycloaddition products are in agreement with their assigned structures.

Cycloadditions of Hexynylcyanoketene to Cinnamylideneamines. General Procedure. A solution of 200 mg (0.57 mmol) of 2,5-diazido-3,6-dihexynyl-1,4-benzoquinone in 50 mL of dry benzene was added dropwise to a refluxing solution of 200 mg (1 mmol) of the cinnamylideneamine in 200 mL of benzene under an atmosphere of nitrogen. After 3 h, the solvent was removed, and the crude product was purified by silica gel chromatography (hexane–ethyl acetate). Spectral properties of the products are in agreement with their assigned structures. See paragraph at end of text for supplementary material.

(*E*)- and (*Z*)-3-Cyano-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone. A solution of 100 mg (0.3 mmol) of **15c** and 0.2 mL of glacial acetic acid in 2 mL of ethyl ether (0 °C) was treated with 39 mg (0.6 mmol) of powdered Zn. After 1.5 h the solution was filtered and washed with water and then with 5% Na_2CO_3. The organic layer was dried and the solvent removed in vacuo. The residue was subjected to preparative thin-layer chromatography (silica gel, 1:9 ethyl acetate–hexane) to give 55 mg (60%) of the titled mixture of diastereomers in a ratio of 1:1: colorless oil; IR (neat, cm^{-1}) 2245, 1765; ^1H NMR ($CDCl_3$) δ 7.40 (s, 5 H), 7.20 (m, 4 H), 6.90 (m, 1 H), 6.30 (m, 1 H), 4.85 (m, 1 H), 4.45 (d, J = 5 Hz, 0.5 H), 3.90 (d, J = 3 Hz, 0.5 H), 3.75 (s, 3 H); mass spectrum (CI), m/e 305. This mixture of cis and trans isomers was used without further purification for the rechlorination to give **15** and **21c**.

(*E*)- and (*Z*)-1-Butyl-3-cyano-4-(2-phenylethenyl)-2-azetidinone. This mixture of diastereomers was prepared from **15d** in 76% yield as a colorless oil by the reductive procedure described above: IR (neat, cm^{-1}) 2220, 1780; ^1H NMR ($CDCl_3$) δ 7.37 (m, 10 H), 6.81 (d, J = 16 Hz, 1 H), 6.20 (dd, J = 16 Hz, 1 H), 4.35 (m, 2 H), 3.75–2.70 (m, 2 H), 1.80–0.70 (m, 7 H); mass spectrum (CI), m/e 255. This mixture of isomers was used without further purification for the rechlorination to give **15d** and **21d**.

3-Cyano-1-(4-methoxyphenyl)-4-(2,2-diphenylethenyl)-2-azetidinone. Reductive dechlorination of **15i** (Zn, CH_3CO_2H) by the method described above gave the titled compound in 89% yield: white crystal, mp 149–150 °C (CH_3OH); IR (Nujol, cm^{-1}) 2240, 1765; ^1H NMR ($CDCl_3$) δ 7.05 (m, 4 H), 6.22 (d, J = 9 Hz, 1 H), 4.75 (dd, J = 9, 6 Hz, 1H), 3.75 (s, 3 H); mass spectrum (CI), m/e 369 (M+1, $C_{24}H_{20}N_2O_2$).

(*E*)- and (*Z*)-1-*tert*-Butyl-3-chloro-3-cyano-4-(2,2-diphenylethenyl)-2-azetidinone. Reductive dichlorination of **18i** (Zn, CH_3CO_2H) by the procedure described above gave an 80% yield of a mixture of the above diastereomers, which were separated by HPLC. *Z* isomer: IR (neat, cm^{-1}) 2240, 1760; ^1H NMR ($CDCl_3$) δ 7.20 (m, 10 H), 5.96 (d, J = 9 Hz, 1 H), 4.35 (dd, J = 3, 9 Hz, 1 H), 3.65 (d, J = 3 Hz, 1 H), 1.33 (s, 9 H). *E* isomer: IR (neat, cm^{-1}) 2240, 1760; ^1H NMR ($CDCl_3$) δ 7.20 (m, 10 H), 6.18 (d, J = 9 Hz, 1 H), 4.35 (dd, J = 6, 9 Hz, 1 H), 3.98 (d, J = 6 Hz, 1 H), 1.35 (s, 9 H).

Chlorination of 3-Cyano-1-(4-methoxyphenyl)-4-(2-phenylethenyl)-2-azetidinone. Preparation of 15c and 21c. A solution of 110 mg (0.39 mmol) of the titled 2-azetidinone in 5 mL of THF (0 °C) was treated with 30 mg (0.60 mmol) of NaH dispersed with mineral oil. After 5 min, 80 mg (0.60 mmol) of *N*-chlorosuccinimide was added. After 15 min, the solution was filtered, washed with brine, dried ($MgSO_4$), and concentrated to give 109 mg (91%) of a mixture of **15c** and **21c**. The observed spectral properties of this mixture were essentially the same as those reported for **15c**. However, the ratio of isomers was obtained from the integration of the absorptions due to the methine proton at position **4** in the 2-azetidinones which appear at δ 4.88 (**15c**) and 5.13 (**21c**) and are in a ratio of, respectively, 7:4.

Chlorination of 1-Butyl-3-cyano-4-(2-phenylethenyl)-2-azetidinone. Preparation of 15d and 21d. The titled compound was chlorinated by the above procedure to give the 2-azetidinones **15d** and **21d** in a ratio of 9:5 (90%) as evidence by the ratio of the methine proton absorption at position 4: δ 4.67 (**15d**) and 4.35 (**21d**).

Chlorination of 3-Cyano-1-(4-methoxyphenyl)-4-(2,2-diphenylethenyl)-2-azetidinone. Preparation of 18i and 23. Chlorination of the *Z* isomer of the titled 2-azetidinone via the above procedure gave **23** and **18i** in a respective ratio of 4:2 (93%). As above, this isomeric ratio was determined by integration of the C-4 methine proton: δ 4.26 (**23**) and 4.57 (**18i**). The same ratio of products was also obtained when the *E* isomer of the starting 2-azetidinone was subjected to the chlorination conditions. Although the diastereomers were not separated, their ratio can be obtained from the spectrum of the mixture. **23**: ^1H NMR ($CDCl_3$) δ 7.20 (m, 10 H), 6.07 (d, J = 9 Hz, 1 H), 4.26 (d, J = 9 Hz, 1 H), 1.35 (s, 9 H).

(*Z*)-3-*tert*-Butyl-3-cyano-4-(hydroxymethyl)-1-(4-methoxyphenyl)-2-azetidinone (25). A solution of 548 mg (1.52 mmol) of **12c** in 20 mL of CH_2Cl_2 (−78 °C) was treated with excess ozone. The solution was then purged with N_2, $NaBH_4$ was added, and the resulting solution was allowed to warm to ambient temperature (30 min). The reaction solution was then treated with 10% HCl (1 mL), washed with water, dried, and concentrated. The residue was then purified by PLC (silica gel, 1:9 ethyl acetate–hexane) to give 302 mg (69%) of **25**: mp 131–132°; ^1H NMR ($CDCl_3$) δ 7.10 (m, 4 H), 4.17 (m, 2 H), 3.78 (s, 3 H), 3.00 (m, 1 H), 1.20 (s, 9 H); mass spectrum (CI, m/e 289 (M + 1).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.94. Found: C, 66.49; H, 7.01.

Cycloaddition of Methylcyanoketene to Cinnamylidene-*p*-methoxyaniline. Preparation of (*Z*)-3-Cyano-1-(4-meth-

oxyphenyl)-3-methyl-4-(2-phenylethenyl)-2-azetidinone (27) and (*Z*)- and (*E*)-3-Cyano-3,4-dihydro-1-(4-methoxyphenyl)-3-methyl-4-phenyl-2(1*H*)-pyridone (28 and 29). A solution of 120 mg (0.55 mmol) of 2,5-diazido-3,6-dimethyl-1,4-benzoquinone and 237 mg (1.0 mmol) of **11c** in 10 mL of anhydrous chlorobenzene was maintained at 130 °C for 1 h. The solvent was then removed and the dark brown residue subjected to PLC (silica gel, 1:9 ethyl acetate–hexane) to give the purified products **27** and **28**. Compound **29** was detected from the ^{1}H NMR of the mixture.

Compound **27**: yield, 8%; colorless oil; IR (Nujol, cm^{-1}) 2230, 1760; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 7.02 (m, 4 H), 6.87 (d, J = 16 Hz, 1 H), 6.28 (dd, J = 8, 16 Hz, 1 H), 4.40 (d, J = 8 Hz, 1 H), 3.70 (s, 3 H), 1.80 (s, 3 H); mass spectrum (CI), m/e 319 (M + 1).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.49; H, 5.66. Found: C, 75.72; H, 5.73.

Compound **28**: yield, 46%; white crystals, mp 144–145 °C; IR (Nujol, cm^{-1}) 1690; ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 5 H), 7.05 (m, 4 H), 6.41 (d, J = 8 Hz, 1 H), 5.38 (dd, J = 4, 8 Hz, 1 H), 3.75 (s, 3 H), 3.70 (m, 1 H), 1.61 (s, 3 H).

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.49; H, 5.66. Found: C, 75.72; H, 5.49.

Dechlorination/Methylation of 15c. Preparation of 27. The β-lactam **15c** (45 mg, 0.148 mmol) was reductively dechlorinated (Zn, CH_3CO_2H) and converted to its enolate (NaH, THF, 0 °C) by the procedures previously described. The solution of the enolate was treated with 0.05 mL of CH_3I, and after 30 min the reaction was quenched with 5 mL of water and extracted with CH_2Cl_2. This solution was dried ($MgSO_4$), the solvent was removed, and the light yellow oil was purified by PLC (1:9 ethyl acetate–hexane) to yield 30 mg (64%) of **27**, which was identical with that formed in the cycloaddition of methylcyanoketene to **11c**.

Dechlorination/Methylation of 16c. Preparation of 28. To a solution of 102 mg (0.30 mmol) of **16c** in 14 mL of acetic acid and 5 mL of THF (0 °C) was added 39 mg (0.60 equiv) of powdered Zn. After 1 h the reaction mixture was filtered and washed with brine, then 10% sodium carbonate, and water. After the mixture was dried, the solvent was removed to yield 79 mg (87%) of the dechlorinated lactam: IR (neat, cm^{-1}), 2240, 1690; ^{1}H NMR ($CDCl_3$) δ 7.25 (s, 5 H), 6.90 (m, 4 H), 6.26 (m, 1 H), 5.22 (m, 1 H), 3.94 (m, 2 H), 3.70 (s, 3 H). This product (61 mg, 0.20 mmol) was dissolved in 3 mL of THF (0 °C) and treated with 20 mg of NaH (50:50 dispersion in mineral oil). After 30 min, 0.5 mL (0.80 mmol) of CH_3I was added, and 20 min later the reaction was quenched with 5 mL of water. The mixture was then extracted with $CHCl_3$ and the organic layer dried ($MgSO_4$). The solvent was removed to yield 58 mg of **28**, which was identical with the product obtained in the cycloaddition of methylcyanoketene to **11c**.

Dechlorination/Methylation of 16c. The above enolate anion, generated from 50 mg of the lactam **16c** was treated with 80 mg (0.60 mmol) of *N*-chlorosuccinimide, and after 20 min the reaction was quenched with 5 mL of water and extracted with $CHCl_3$. After the mixture was dried ($MgSO_4$), the solvent was removed to yield 92% of the lactam **16c**, which was identical with the product obtained from the cycloaddition of CCK to **11c**.

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Supplementary Material Available: Full NMR and IR data for compounds **3**, **4**, **6**, **7**, **9**, **10**, and **12–20** and atomic coordinates for **25** (22 pages). Ordering information is given on any current masthead page.

Nicotinic Acid Lariat Ethers: Syntheses, Complexation, and Reduction

George R. Newkome* and Charles R. Marston

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803-1804

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Combination of 2-(hydroxymethyl)-5-oxazolinylpyridine **16a** with lariat ethers **21** and **23** generated chiral 6-methylnicotinic oxazoline lariat ethers **22** and **24**, respectively. Chiral lariat ether **24b** by stereoselective metal-directed addition of methylmagnesium bromide was converted to the corresponding enantiomerically enriched *N*-magnesio-1,4-dihydropyridine **26**. Lariat **26** and the nonlariat analogue **31** both reduced α,α,α-trifluoroacetophenone in a NADH model-like reduction to give the *S* alcohol **32** in low enantiomeric excess.

Metal ion participation in the in vivo stereospecific NADH-mediated hydride reduction of carbonyl substrates has been well established.[1] Likewise, by incorporation of various metal ions into "chiral models", dramatic enhancements in the stereospecificity of carbonyl reductions have been observed.[2] A rationale for the improved selectivity of hydride reduction by chiral NADH models in the presence of magnesium ion was put forward by Ohno et al.,[2,3] in which he proposed the involvement of a three-step mechanism: (1) initial electron transfer, (2) proton transfer, and (3) electron transfer. This overall

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